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phage display, and combinatorially derived proteins from ribosome display.

24. (New) The method of claim 3, wherein the nucleic acids are aptamers.

REMARKS

The Official Action of March 27, 2002, and the prior art cited and relied upon therein have been carefully reviewed. The claims in the application are now claims 1-7, 13-15, and 17-24, and these claims define patentable subject matter warranting their allowance. Favorable reconsideration and such allowance are respectfully urged.

Briefly, this invention relates to sensitive rapid and convenient assays for detection and quantification of one or several analytes in solution using proximity probes. This method depends on the simultaneous and proximate recognition of target molecules by pairs of affinity probes, which results in a detection signal capable of amplification. A recent article summarizing the work of this invention appears in the May 2002 issue of the prestigious journal Nature Biotechnology and is attached to this response.

Claims 1-7 and 13-18 stand rejected under 35 U.S.C. 112, second paragraph, for being indefinite. This rejection is respectfully traversed.

The Examiner refers to claim 37 as containing confusing language. Applicants assume the Examiner is referring to claim 1 (there is no claim 37), and have amended it accordingly and introduced new dependencies.

The Examiner further holds that claims 13-18 are incomplete sentences which do not indicate the subject matter clearly and are indefinite for depending on non-elected claims and that claim 3 is indefinite in its use of language. These rejections are respectfully traversed insofar as they are understood[1].

Claim 16 has been canceled (its subject matter is covered by claim 13). Claims 3 and 13-18 have been amended and claims 19-22 have been added to better particularly point out and distinctly claim the subject matter which the applicants regard as their invention. Applicants believe that the amendments presented above address all the points raised in the rejection, and therefore respectfully request withdrawal of the rejection.

Claims 1-7 and 13-15 stand rejected under 35 USC 102(b) as being anticipated by Landegren WO 97/00446. This rejection is respectfully traversed.

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[1] The rejections do not explain sufficiently what the examiner considers is wrong with the claims. Claims are not sentences.

The Landegren reference teaches both an immobilization step and a washing step (see, e.g., page 3, last paragraph; page 4, first paragraph; Figure 1). Neither step is required in the claimed invention. The reaction in the present application takes place wholly in solution and no washing step is required. Claim 1 recites "analyte(s) in solution" to mean that the analyte(s) remain *free in solution throughout the assay and are not immobilized on a solid support*, as disclosed by the cited reference. There is no anticipation of applicants' claims.

Withdrawal of the rejection is therefore respectfully requested.

Claims 1-3, 5, 7, 14 and 17-18 stand rejected under 35 USC 102(b) as being anticipated by Landegren et al (U.S. Patent No. 4,988,617). This rejection is respectfully traversed.

Applicants contend that although the term "binding moiety" is used in both the claimed invention and in the cited prior art, it is used for different purposes and subject matter. The binding moiety, as exemplified by biotin, attached to an oligonucleotide as described in the '617 patent, is used for a separation process. In such a process, the biotin moiety is captured by a second immobilized binding moiety, such as streptavidin bound to a solid support. This

process is designed to exploit the well-known binding affinity of biotin for avidin. The "binding moiety" of the '617 patent, however, never binds to the analyte molecule, whereas in the claimed invention the term "binding moiety" describes a moiety which does bind the target analyte. An *immobilization* step is also disclosed and is central to the invention of the cited reference. There is therefore no anticipation.

Thus, reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1-3, 5, 7, 14 and 16 stand rejected under 35 USC 102(b) as being anticipated by Landegren et al (U.S. Patent No. 5,871,921). This rejection is respectfully traversed.

Contrary to the Examiner's assertion that the "intermediate segments" referenced in the cited patent are binding moieties, Applicants point out that said segments are not binding moieties. In the '921 patent, the "intermediate segments" described are again not to be used as binding moieties in the sense used in the instant invention, because they do not bind to the target analyte. The intermediate segments only link the two nucleic acid parts of the probe. Such an intermediate segment only enables the circularization of the probe upon target binding, hybridization and catenation. Again, there is no anticipation.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Favorable consideration is earnestly solicited.

Respectfully submitted,

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Version with Markings to Show Changes Made

1. (Amended) A method for detecting ~~and/or quantifying~~ one or more analyte(s) in solution, characterised by

a) binding of two or more proximity probes to a respective binding site on said analyte(s), wherein the proximity probes are comprised of a binding moiety and ~~a~~ thereto coupled nucleic acids;

b) allowing the binding moiety to bind to the analyte(s) and allowing the nucleic acids to interact with each other if they are in close proximity to each other; and

c) detection ~~and/or quantification~~ of the degree of interaction between the nucleic acids with the proviso that the binding moiety~~ies~~ and the analyte(s) not all comprise nucleic acid.

2. (Amended) A method according to claim 1, further comprising amplification of the interacted nucleic acids and ~~detection/~~quantification of the amplification product.

3. (Amended) A method according to claim 1, wherein the binding moiet~~ies~~y of the proximity probes ~~are selected~~is selected from the group consisting of ~~a~~ proteins, ~~such as a monoclonal or polyclonal antibody, lectin, soluble~~

~~cell surface receptor, combinatorially derived protein from phage display or ribosome display,~~ peptides, carbohydrates, nucleic acids~~, such as an aptamer, or~~ and combinations thereof.

13. (Twice Amended) ~~Method~~ A method according to claim 1 for screening for ligand-receptor interaction antagonists in a high throughput screening procedure, wherein a drug candidate molecule is screened for ability to disrupt proximity between the proximity probes.

14. (Twice Amended) ~~Method~~ A method according to claim 1, wherein the first proximity probe is comprised of purified analyte coupled to an oligonucleotide and the second proximity probe is comprised of a binding moiety specific for the analyte with a coupled oligonucleotide capable of interacting with the first proximity probe ~~for competitive detection and/or quantification of an unknown analyte in solution~~.

15. (Twice Amended) ~~Method~~ A method according to claim 13 wherein the drug candidate molecule is a biomolecule derived from a library of potential ligands to one of the binding sites involved in the formation of the proximity between the proximity probes ~~for screening ligand candidates in a large pool~~.

17. (Twice Amended) ~~Method~~ A method according to claim 1 ~~for~~, comprising using said method for the detection of infectious agents.

18. (Twice Amended) ~~Method~~ A method according to claim 17, wherein the infectious agents ~~is~~ are ~~—~~detected in food for humans and animals.